REMARKS

This document is submitted in response to the Office Action of May 05, 2003. Pending claims 1-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Qiu *et al.* (U.S. Patent No. 6,346,679) or Qiu *et al.* (U.S. Patent No. 6,133,440) in view of Hansen *et al.* (U.S. Patent No. 5,254,174) or DeFrees (U.S. Patent No. 6,454,946) and claims 1-21 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,436,679 in view of Hansen *et al.* (U.S. Patent No. 5,254,174) or DeFrees (U.S. Patent No. 6,454,946). Each of these rejections is discussed below.

Rejection under 35 U.S.C.§ 103(a)

The Examiner has rejected claims 1-21 under 35 U.S.C. § 103(a) as being unpatentable over Qiu *et al.* (U.S. Patent No. 6,346,679) or Qiu *et al.* (U.S. Patent No. 6,133,440) in view of Hansen *et al.* (U.S. Patent No. 5,254,174) or DeFrees (U.S. Patent No. 6,454,954). The Examiner provides that each of the '679 and '440 patents disclose the precise process recited in Applicant's claims, with the exception of the nanofiltration step as recited in step (e). The Examiner further provides that Hansen *et al.* and DeFrees disclose that at the time of Applicant's invention it was known to be advantageous to treat polysaccharide-containing compositions of the type disclosed in the '679 and '440 patents by nanofiltration to remove impurities. From this the Examiner concludes that an artisan of ordinary skill would have been motivated to have included a nanofiltration step to the processes in the '679 and '440 patents.

The Examiner bears the burden of establishing a prima facie case of obviousness. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Once a *prima facie* case of obviousness is established by the Examiner, the burden then shifts to Applicant to rebut that case. A showing of unexpectedly improved results is one way to rebut a *prima facie* case of obviousness. In re Dillon, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

The present application is a continuation in part of U.S. Patent Application Serial No. 09/295,907, filed April 21, 1999, now U.S. Patent No. 6,436,679, which is a divisional of U.S. Patent Application Serial No. 09/169,449, filed October 9, 1998, now U.S. Patent No. 6,133,440. The present application rests on the teachings of each of these applications and therefore Applicant maintains that neither of these references is prior art to the present application. The Examiner notes Applicant claims to priority to each of these applications, but has determined that at least one of these applications is "to another," since it has different inventive entities. In response, Applicant agrees to submit a Declaration pursuant to 37 CFR § 132 establishing that any unclaimed invention described in the issued patents --U.S. Patent No. 6,436,679 and U.S. Patent No. 6,133,440-- was conceived by at least one of the inventors commonly named in said patents and the present application.

In the alternative, for the reasons discussed in detail below, Applicant maintains that neither Hansen *et al.* nor DeFrees render the method of the instant invention obvious.

The Hansen *et al.* Patent (U.S. Patent No. 5,254,174)

Hansen *et al.* teach a method for preparing a mixture of fructose (F), glucose (G) and compounds of the general formula GF_n, wherein n is an integer. (Hansen *et al.*, col. 1, lines 6-10). The method described by Hansen *et al.* is comprised of the steps of preparing a plant extract; treating the plant extract with $Ca(OH)_2$, CO_2 or phosphoric acid to a pH of 8.0-9.5 and filtering to remove impurities, such as pectin, proteins and cell material; performing ion exchange chromatography (both cation and anion) to remove charged impurities such as salts; optionally treating with active carbon to decolorize; optionally concentrating by hyperfiltration; and further purification by chromatography or ultrafiltration or both. Thus, the Hansen *et al.* patent teaches a method for preparing a mixture of fructose and glucose comprising three purification steps: 1) precipitation of

impurities with a base; 2) purification by ion exchange chromatography and finally 3) purification by chromatography, ultrafiltration or both. As provided in the Abstract of the Invention, "[t]he mixture is recovered from plant tubers or roots by means of a method which does not involve any chemical modification of the components of the mixture." (Abstract, emphasis added).

As noted by the Examiner, the method of Hansen *et al.* includes a nanofiltration step to reduce the amount of fructose, glucose and sucrose. Thus, the nanofiltration is performed on a mixture, isolated from a plant source, which has not been chemically modified to remove low molecular weight mono and disaccharides, such as glucose, fructose and sucrose. It is not clear from the Hansen *et al.* reference on what scale the purification is being performed.

The DeFrees Patent (U.S. Patent No. 6,454,954)

Defrees teaches a method for purifying a specific carbohydrate or oligosaccharide from a solution containing contaminants by use of nanofiltration. In a typical application, the saccharides of interest are retained by the nanofiltration membrane and the contaminants pass through. Briefly, with reference to the examples, a carbohydrate is first synthesized. If the sample contains proteins, the proteins are removed by ultrafiltration. (Specification, col. 8 lines1-31). Salts and other low molecular weight contaminants are then removed by a method selected from nanofiltration or reverse osmosis. With reference to the examples, which begin in column 17 of the Specification, the purification is being performed on a small scale. For example, the results provided in Table 3 were obtained using a sample volume of 50 mL. (Specification, Table 3, col. 21).

DeFrees provides that the method can be applied to "separating oligosaccharides from enzymes and/or other components of reaction mixtures used for enzymatic synthesis or enzymatic degradation of oligosaccharides." (Specification, col. 5, lines 15-18). However, no examples of the purification of mixtures resulting from enzymatic degradation are described. All of the examples provided involve the purification of oligosaccharides that have been prepared using enzymatic synthesis, specifically

enzymatic synthesis using glycosylytransferases, more specifically enzymatic synthesis using a sialyltransferase. Glycosyltransferases are enzymes which catalyze the transfer of sugar moieties from activated donor molecules to specific acceptor molecules. Sialyltransferases catalyze the transfer of a sialylic acid to a saccharide.

The present invention is drawn to a method for preparing an activated mixture of polysaccharides. The method is comprised of (a) extracting Aloe gel juice from Aloe; (b) performing a controlled limited hydrolysis of the polysaccharides in the aloe juice; (c) terminating the hydrolysis; (d) optionally decolorizing and filtering the hydrolyzed product and finally (e) purifying the hydrolyzed product by nanofiltration. The product obtained following nanofiltration is at least twice as pure as the product obtained by precipitation from ethanol as described in Example 3. (Specification, page 15, line 17-page 16, line 4).

The method of this invention provides a unique complex mixture of polysaccharides, which does not exist in nature and which is obtained by a controlled limited enzymatic hydrolysis of an extract isolated from an Aloe plant. As provided in the Specification, the composition of matter prepared by the method of this invention has increased stability and immunomodulatory activity. (Specification, page 4, lines14-16). Thus, the present invention describes a complex composition of matter that has been prepared in a specific manner in order to maximize the biological activity of the composition. (Specification, page 15, line 28 - page 16, line 6, and Figure 4). The average molecular weight of the polysaccharides in the composition of matter prepared by the method of this invention is 70,000-80,000 Da with a range between 50,000 and 200,000 Da.

Thus, the present invention teaches a novel method for preparing a novel composition of matter. The Examiner provides that Hansen *et al.* and DeFrees disclose that at the time of Applicant's invention it was known to be advantageous to treat polysaccharide-containing compositions of the type disclosed in the '679 and '440 patents by nanofiltration to remove impurities. From this the Examiner concludes that an artisan of ordinary skill would have been motivated to have included a nanofiltration step to the processes in the '679 and '440 patents. Contrary to this assertion, Applicant maintains,

for the reasons discussed above, that neither Hansen *et al.* nor DeFrees describes the purification by nanofiltration of compositions of the type disclosed in the instant specification. Therefore, Applicant maintains that neither Hansen *et al.* nor DeFrees render the method of the present invention obvious.

It is well known that most organic compounds that are available from natural, as well as synthetic sources, are present as complex mixtures. Over the years scientists have developed a number of useful general methods for the purification of these mixtures. These methods of purification include techniques such as extraction, recrystallization, distillation, sublimation, various types of chromatography including, but not limited to, column chromatography, preparative gas chromatography, preparative hplc, and preparative thin layer chromatography and various methods of ultrafiltration including, but not limited to, nanofiltration. Applicant maintains that the reason that so many general methods have been developed is that a particular method will not necessarily be an effective method of purification in all cases. Thus, the general method of purification selected to purify a specific mixture is highly dependent on the mixture to be purified and will generally involve at least some amount of experimentation to tailor the general method to the specific purification being performed.

Thus, assuming for the sake of argument that it may have been obvious to try to purify the instant composition of matter using any of the known general methods of purification, including purification by nanofiltration, there is absolutely no evidence provided in either of the cited references that this unique composition of matter could successfully be purified by nanofiltration. As noted above, both the suggestion and the expectation of success must be found in the prior art. Additionally, obtaining a product that is at least twice as pure as the product obtained by precipitation from ethanol was completely unexpected because the nanofiltration was performed on a much larger scale than the precipitation from ethanol (50 g vs. 220 kg).

Applicant maintains therefore that none of the references either alone or in combination render the method of this invention obvious and therefore respectfully requests that this rejection be withdrawn.

Double Patenting Rejection

The Examiner has rejected claims 1-21 as being unpatentable over claims 1-10 of U.S. Patent 6,346,679 in view of Hansen *et al.* (U.S. Patent No. 5,254,174) or DeFrees (U.S. Patent No. 6,454,946). In response to this rejection, a Terminal Disclaimer is being submitted with this document as required by the Examiner.

Common Ownership

The Examiner provides that commonly assigned U.S. Patent No. 6,436,679 would form the basis for a rejection of claims 1-21 of the instant invention under 35 U.S.C. § 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g). The Examiner has provided that a showing that the inventions of U.S. Patent No. 6,346,679 and the instant case were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. §§102(f) or (g) or 35 U.S.C. § 102 (e). In response to this rejection, included with this document are copies of the recorded assignments for each of these cases (as set forth below) showing that both inventions are commonly owned. (37 C.F.R. § 1.104(a)(5)(ii)).

1. Copy of the Assignment from inventors Z. Qiu, B. Mahiou, A. Padmapriya and T. Farrow to Unigen Pharmaceuticals, Inc. for U.S. Patent Application Serial No. 10/039,752.

2. Copy of the Assignment from inventors Z. Qiu and B. Mahiou to Univera Pharmaceuticals, Inc. for U.S. Patent Application Serial No. 09/169,449 (now U.S. Patent No. 6,133,440). U.S. Patent No. 6,346,679 is a division of U.S. Patent Application Serial No. 09/169,449 (now U.S. Patent No. 6,133,449).

3. Copy of the Change of Name from Univera Pharmaceuticals, Inc. to Unigen Pharmaceuticals, Inc.

If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: September 5, 2003

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